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KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/403,440	LANE, DAVID PHILIP	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,8 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant amends claim 1 directed to an in vitro method for disrupting the binding of p53 and mdm2, or inhibiting the production of mdm2 in a population of cancer cells, in which mdm2 is not overexpressed.

Since applicant has elected Group I, a method for preventing or treating a condition, comprising disrupting the binding of human p53 and mdm2, for action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, the embodiments of claims 1-3, 8, 11, directed to an in vitro method for inhibiting the production of mdm2, have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. 1.142(b) and M.P.E.P. 821.03.

Newly amended claims 1-3, 8, 11, directed to an in vitro method for inhibiting the production of mdm2, are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

According to PCT Rule 13.2, unity of invention exists only when the shared same or correponding techinical feature is a contribution over the prior art. The amended claims 1-3, 8, 11, directed to an in vitro method for inhibiting the production of mdm2, which belong to group II, do not relate to a single general inventive concept because they lack the same or corresponding special technical feature. The technical feature of group I, directed to a method for disrupting the binding of p53 and mdm2, is known in

the art (see 103 rejection below) and thus does not make a contribution over the prior art.

Accordingly, claims 1-3, 8, 11, SEQ ID NO:4, as directed to an in vitro method of disrupting the binding of p53 and mdm2, are being examined.

The amended claims 1-3, 8, 11, SEQ ID NO:4, as directed to an in vitro method of inhibiting the production of mdm2, is withdrawn from consideration, because they belong to the non-elected invention of group II, for reasons set forth above.

The following are the remaining rejections.

OBJECTION

1. Claims 1-3, 8, 11 are objected to because part of claims 1-3, 8, 11 are drawn to non-elected invention.

2. Claims 1-3, 8, 11 are objected to for the use of the language "mdm2" as the sole means of identifying the protein for use in the claimed method, because different laboratories may use the same laboratory designations to define completely distinct proteins. Amendment of the claims to include physical and/or functional characteristics of mdm2, which unambiguously define mdm2 is required.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION, NEW REJECTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art

can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 1-3, 8, 11 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 1-3, 8, 11 are drawn to :

1) An in vitro method for inducing growth inhibition or apoptosis in a population of cancer cells in which mdm2 is not overexpressed, comprising administering an agent comprising a peptide, less than 25 amino acids in length, and including the peptide motif "**F**XaaXaaXaa**W** (SEQ ID NO:4)", wherein Xaa is any amino acid, and wherein said agent has the property of disrupting the binding of p53 and mdm2 (claim 1).

2) The method of claim 1, wherein the p53 is activated for DNA specific binding and transcription (claim 2).

3) The method of claim 1, wherein said agent could comprise a peptide having an amino acid sequence that consists of a portion of human p53 which have the property of binding to mdm2 (claim 3).

4) The method of claim 1, wherein the agent has the property of competing with mdm2 for binding p53, but does not inhibit DNA specific binding property of p53 (claim 8).

5) The method of claim 1, comprising administering an agent comprising a peptide, less than 25 amino acids in length, and including the peptide motif FXaaXaaXaaW (SEQ ID NO:4), wherein the peptide has at least 70% amino acid sequence identity with a portion of human p53 (claim 11).

The specification discloses that in ELISA assays, the synthetic peptide of SEQ ID NO:3 or peptide, or TIP 12/1 could strongly inhibit the binding of p53 and mdm2 at an inhibitory IC50 of 100 nM or 300 nM, as compared to 400 nM of the full length p53, and 2000 or 15000 nM of the wild type p53 peptide consisting of residues P13-N29 of SEQ ID NO:2 or TIP (p. 24-25, table 1 on page 35). The specification discloses that microinjection of TIP12/1 of SEQ ID NO:3 into a cell line, that expresses low level of wt p53 and no mdm2 elevation, strongly induces the p53 reporter, at a level comparable to p53 induction by UV, indicating a strong inhibition of interaction between mdm2 and p53, as compared to low level of induction of p53 by the wild type p53 peptide of SEQ ID NO:2 (p.26-29).

Claims 1-2, 8 encompass variants of SEQ ID NO:3, of any length less than 25 amino acids, provided they contain the motif FXaaXaaXaaW (SEQ ID NO:4), wherein Xaa is any amino acid, and wherein the amino acids flanking the motifs could be any amino acid.

Claim 3 encompasses any portion of p53 of less than 25 amino acids in length, which has the motif FxaaXaaXaaW, and which does not necessarily comprise SEQ ID NO:2. The specification, however, only discloses a single peptide portion of p53, SEQ ID NO:2, which has the motif FxaaXaaXaaW.

Claim 11 encompass variants of the wild type p53 peptide of SEQ ID NO:2 of any length less than 25 amino acids, provided they contain the motif FXaaXaaXaaW (SEQ ID NO:4), wherein Xaa is any amino acid, and wherein the amino acids flanking the

motifs could be any amino acid, and wherein the variants have 70% identity with any fragment of p53.

It is noted that the critical function , which represents the claimed invention, is to disrupt the binding of p53 and mdm2 with an adequate strength, resulting in an adequate amount of activated p53, similar to p53 induction by UV, wherein a sufficient amount of activated p53 could induce cell cycle arrest or apoptosis in cells, similar to the effect of UV damage (specification, p.1, second paragraph, and p.26-29).

A. There is no correlation between structure of the peptide for use in the claimed method and critical function, because the motif FXaaXaaXaaW (SEQ ID NO:4) per se does not confer said critical function.

Bottger V at al, Oncogene, 1996, 13: 2141-2147, IDS# 5 submitted on 09/06/2000, of record, teach that the oncogene mdm2 and its human homologue hdm2 bind to the tumor suppressor protein p53 and inactivates its function as a positive transcriptional factor (abstract). Bottger et al teach that specific activity of various synthetic peptides, having the common motif "**F**XaaXaaXaa**W**, as inhibitors of the hdm2-p53 interaction **varies over 100 fold** range (p.2144, first column, first paragraph, table 1 on page 2142, and figure 5 on page 2144). Bottger et al further teach that phage clone 12/1 (the sequence 12/1 on table 1 on page 2142), the most potent inhibitor, contains the motif PX**F**XDY**W**XXL, wherein **each of the selected consensus residue is important for the maximum strength of interaction with hdm2** (p.2144, first column, first paragraph). Bottger V at al further teach that the **L** of the wt p53 sequence TFSDL**W** is important for hdm2 binding and that the Tyrosine (Y), not found in the wild

type, is selected over the wild type L in phage display increases the inhibitory activity, probably as additional binding points for hdm2, for improved stability of the peptide or its better conformational fit into the hdm2 binding pocket (p.2144, second column, third paragraph).

Thus based on the teaching in the art, except for TIP12/1 comprising SEQ ID NO:3 inserted in thioredoxin, or the motif PX**F**XDY**W**XXL taught by the art, one cannot predict that any other peptides sharing the motif **F**XaaXaaXaa**W**, including the wt p53 peptide of SEQ ID NO:2, would have adequate strength of interaction with hdm2 to displace an adequate numbers of the wild type full length, endogenous p53 molecules from binding to the inhibitor hdm2, such that the activity of p53 is adequately induced, resulting in cell cycle arrest or apoptosis, because of the following reasons:

a) The activity of the synthetic peptides sharing the motif **F**XaaXaaXaa**W** (SEQ ID NO:4) could have an inhibitory activity difference as much as over 100 fold-range (see table 1, phages 12/1-5, on page 2142, and p.2144, first column, first paragraph in Bottger et al), and

b) The wild type full length p53 has an inhibitory value IC50 of 400 nM, versus an IC50 of 100 nM or 300 nM for the most potent inhibitor, TIP12/1, whereas even the wild type p53 peptide sequence of SEQ ID NO:2 (TIP) has only an IC50 of 15000 nM, as disclosed in the specification.

In other words, In view of the strong binding of the wild type full length p53 to mdm2, as compared to that of even the most potent inhibitor, TIP 12/1, one cannot predict that other claimed peptides sharing the motif **F**XaaXaaXaa**W** (SEQ ID NO:4)

would have an adequate inhibitory activity to displace an adequate number of the wild type full length endogenous p53 molecules from binding to mdm2, such that the activity of p53 is adequately induced, resulting in cell cycle arrest or apoptosis.

In view of such unpredictability, the motif FXaaXaaXaaW (SEQ ID NO:4) does not confer the critical function, and there is no correlation between structure of the claimed peptide and critical function.

B. Further, the claims encompass peptides of any length, provided they are less than 25 amino acids, for example hexapeptides, or those peptides having less 10 amino acids.

Bottger et al teach that no mdm2 binding phage could be isolated from hexapeptide library, and that hexapeptides cannot provide sufficient correctely spaced contact points to bind to the mdm2 binding pocket with high enough affinity (p.2144, second column, paragraph before last), and

Further, peptides of any amino acids in length, such as those having less than 10 amino acids, would not contain the consensus residues such as P at the position 1 and/or L at position 10, found in the phage motif PX**F**XDY**W**XXL, wherein such consensus residues are necessary for providing the strength of interaction with hdm2, similar to that found in the clone 12/1 (IP3), as taught by Bottger et al (p.2144, first column, first paragraph).

In view of such unpredictability, there is no correlation between structure of the claimed peptide and critical function.

Further, the single disclosed peptide of SEQ ID NO:3, that could adequately disrupt and displace p53 from binding to mdm2, resulting in sufficient increase in the level of p53, similar to that induced by UV, **is not a representative species of the claimed genus of peptides for use in the claimed method.**

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of the variant peptides, as shown in the example of Lilly by structurally describing a representative number of or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, as shown in the example of Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the variant peptides in a manner that satisfies either the standards as shown in the example of Lilly or Enzo. The specification does not provide the complete structure of any variant peptide, that could adequately disrupt the binding of p53 and mdm2, other than SEQ ID NO:3, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single peptide, SEQ ID

NO:3, this does not provide a description of the peptide variants that would satisfy the standard as shown in the example of Enzo.

The specification also fails to describe the peptide variants, by the standards shown in the example in Lilly. The specification describes only a single peptide SEQ ID NO:3. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not meet the 112, first paragraph written description requirement. The specification does not provide an adequate written description of the peptide variants that is required to practice the claimed invention, and one of skill in the art would reasonably conclude that Applicant did not have possession of the claimed variants at the time the invention was made.

Since the specification fails to adequately describe the product for use in the claimed method, it also fails to adequately describe the claimed method.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

I) Claims 1-3, 8, 11 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vitro method for disrupting the binding of p53 and mdm2 in cancer cells that do not overexpress mdm2, comprising administering the peptide consisting of SEQ ID NO:3, does not reasonably provide enablement for an in vitro method disrupting the binding of p53 amd mdm2 in cancer

cells in which mdm2 is not overexpressed, comprising administering an agent comprising a peptide, less than 25 amino acids in length, and including the peptide motif "FXaaXaaXaaW (SEQ ID NO:4)", wherein said agent could comprise a peptide having an amino acid sequence that consists of "a portion of human p53 which have the property of binding to mdm2", or wherein said agent could comprise a peptide at least "70% amino acid sequence identity" with "a portion of human p53", for reasons already of record in paper of 02/22/05.

A. Applicant argues that the fact that some peptides within the scope of the claims might be more potent than others is not sufficient to establish a prima facia case of lack of enablement.

Applicant argues that in the entire rejection, the Examiner seems to be unduly concerned about the claims might include inoperative species.

Applicant's arguments in paper of 08/22/05 have been considered but are found not to be persuasive for the following reasons:

Except for the peptide consisting of SEQ ID NO:3, one cannot predict whether the claimed peptides would have adequate inhibitory activity to displace an adequate number of p53 from binding to mdm2, resulting in a sufficient increase in the induction of p53 activity, similar to p53 induction by UV, such that cell cycle arrest or apoptosis could be induced.

It is noted that although some peptides sharing the motif FXaaXaaXaaW (SEQ ID NO:4) could have some inhibition of the binding of p53 and mdm2, such inhibitory activity is significantly lower than that of SEQ ID NO:3, as much as over 100 fold-range

(see table 1, phages 12/1-5, on page 2142, and p.2144, first column, first paragraph in Bottger et al, of record).

Thus, contrary to Applicant's arguments, the Examiner is not concerned that the claims might include inoperative species. On the contrary, except for a single operative species, SEQ ID NO:3, the claims encompass a genus of species, the critical function of which could not be predicted, in view of the teaching of Bottger et al, of record; i.e. one cannot predict whether the claimed peptides would have adequate inhibitory activity to displace an adequate number of p53 from binding to mdm2, resulting in a sufficient increase in the induction of p53 activity, similar to p53 induction by UV, such that cell cycle arrest or apoptosis could be induced.

In other words, one cannot extrapolate the critical function of a single operative species, SEQ ID NO:3, to that of the claimed genus of species, because there is no correlation between structure and function, supra.

B. Concerning the claimed peptides of less than 10 amino acids in length, Applicant argues that the use of agents which do not have the properties of disrupting the binding of p53 and mdm2 is not within the scope of the claims. Applicant argues that screening for agents of the specified structure, which additionally has the specified biological property might require some experimentations, such experimentation is merely routine and is not undue.

Applicant's arguments in paper of 08/22/05 have been considered but are found not to be persuasive for the following reasons:

The claims clearly encompass a method for inhibiting the binding of p53 and mdm2, using a genus of sequences of any length less than 25 amino acids, including hexapeptides, or ten amino acid peptides, that comprise the peptide motif "FXaaXaaXaaW (SEQ ID NO:4) of 5 amino acids in length.

The function of such claimed peptides however could not be predicted, in view of the teaching of Bottger et al, of record, that no mdm2 binding phage could be isolated from hexapeptide library, and in view that peptides of any amino acids in length, such as those having less than 10 amino acids, would not contain the consensus residues such as P at the position 1 and/or L at position 10, found in the phage motif PX**F**XDY**W**XXL, wherein such consensus residues are necessary for providing the strength of interaction with hdm2, similar to that found in the clone 12/1 (IP3), as taught by Bottger et al (p.2144, first column, first paragraph).

In view of such unpredictability, it would be undue experimentation for one of skill in the art to screen for the peptides for use in the claimed method.

Further, screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays, and by inference suggestions of structural analysis, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

In addition, in view of such unpredictability, one would not know how to use the claimed method as broadly as claimed, and it would be undue experimentation for one skill in the art to practice the claimed invention.

C. Applicant again refers to US 6,153,391, which includes claims to methods that involve generically defined compounds, even including small molecules, that bind to mdm2 and interfere with its binding to p53. Applicant argues that while Applicant appreciates that each case is examined on its own merits, examination cannot entirely disregard the results of the examination of applications of similar disclosure of a closely related field.

Applicant's arguments in paper of 08/22/05 have been considered but are found not to be persuasive for the following reasons:

It is well settled that whether similar claims have been allowed to others is immaterial. See In re Giolito, 530 F.2d 397, 188 USPQ 645 (CCPA 1976) and Ex parte Balzarini 21 USPQ2d 1892, 1897 (BPAI 1991).

II) If Applicant could overcome the above 112, first paragraph, **claims 3, 11 still remain rejected under 112, first paragraph for lack of enablement for an in vitro method of disrupting the binding of p53 and mdm2 of claim 1, wherein the peptide consists of " a portion of human p53" that is necessary for mdm2 binding, or wherein the peptide has at least 70% amino acid sequence identity with "a portion" of human p53.**

Applicant argues that the rejection is legally incorrect, because if claim 1 is enabled, claims 3, 11, which are narrower in scope, are also enabled.

Applicant's arguments in paper of 08/22/05 have been considered but are found not to be persuasive for the following reasons:

Contrary to Applicant's arguments, the rejection is legally correct, because claims 3, 11 are directed to non-enabled specific species of claim 1, even if claim 1 is enabled.

It is noted that a portion of p53 encompasses any portion of p53. Other than SEQ ID NO:2 of the wild type p53, that is less than 25 amino acid in length, and comprises the motif FXaaXaaXaaW (SEQ ID NO:4), one cannot predict there exists any other portion of human p53, such as wild type and variant p53, that is less than 25 amino acid in length, and comprises the motif FXaaXaaXaaW (SEQ ID NO:4).

Further, it is noted that the method of disrupting the binding of p53 and mdm2, using the wild type p53 peptide of SEQ ID NO:2, or its 70% variants thereof, is not enabled because one does not know how to use the claimed method, in view that it is unpredictable that the wild type p53 peptide of SEQ ID NO:2, or its 70% variants thereof could adequately disrupt he binding of p53 and mdm2, such that an adequate amount of p53 could be displaced from the inhibitory mdm2, resulting in sufficient induction of cell cycle arrest or apoptosis, for the reasons set forth above, and in previous Office action.

REJECTION UNDER 35 USC 103, NEW REJECTION

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject

matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bottger et al, 1996, Oncogene, 13: 2141-2147, of record, in view of McCann A H et al,

1995, British J Cancer, 71(5): 981-5, or Quesnel B et al, 1994, Brit J Haematology, 88: 415-418, and further in view of Lee JM et al, 1995, Cancer and metastasis Review, 14(2): 149-161.

Claims 1-2, 8 are drawn to:

1) An in vitro method for inducing growth inhibition or apoptosis in a population of cancer cells in which mdm2 is not overexpressed, comprising administering an agent comprising a peptide, less than 25 amino acids in length, and including the peptide motif "**F**XaaXaaXaa**W** (SEQ ID NO:4)", wherein Xaa is any amino acid, and wherein said agent has the property of disrupting the binding of p53 and mdm2 (claim 1).

2) The method of claim 1, wherein the p53 is activated for DNA specific binding and transcription (claim 2).

3) The method of claim 1, wherein the agent has the property of competing with mdm2 for binding p53, but does not inhibit DNA specific binding property of p53 (claim 8).

Bottger et al teach that the oncogene mdm2 and its human homologue hdm2 bind to the tumor suppressor protein p53 and inactivates its function as a positive transcriptional factor, and that the mdm2-p53 interaction is a much persued target for the development of anti-cancer drugs (abstract).

Bottger et al teach a peptide, clone 12/1, having the consensus PX**F**XDY**W**XXL, could significantly inhibit the binding of p53 and mdm2, even at a peptide concentration of about 0.1 uM or lower, a great increase affinity over the native p53 sequence TFSDLW taught by Picksley et al, or Thut et al (abstract, p. 2141, second column, first

paragraph, figure 5 on page 2144, table 1 on page 2142, p.2144, and p.2146, second column, paragraph under peptides and monoclonal antibodies).

Bottger et al further teach that the peptide represents a clear route towards the design of small synthetic molecules that will restore p53 function in human tumors (p.2141, second column, first paragraph), in view that mdm2 binds to p53 and inactivates its function as a transcriptional factor (p.2141, first column).

Bottger et al also teach that the peptide was selected for improved stability and for its better conformational fit into the hdm2 binding pocket of p53, to displace the binding of p53 to hdm2 (p.2144, second column, last four lines of the third paragraph).

It is noted that the consensus sequence PX**F**XDY**W**XXL taught by Bottger et al is a peptide that is less than 25 amino acid in length, and has the motif **F**XaaXaaXaa**W** (SEQ ID NO:4)", wherein Xaa is any amino acid, of the peptide in the claimed method.

Bottger et al do not teach an in vitro method for disrupting the binding of p53 and mdm2 in a population of cancer cells in which mdm2 is not overexpressed.

McCann et al teach expression of mdm2 expression in breast carcinoma and its association with low level of p53 (abstract, lines 7-9, p.983, first column, last paragraph, last 7 lines). McCann et al teach that mdm2 amplification only occurs at a low frequency in breast cancer, as compared to non-epithelial tumors, and that in one of the amplified samples, there is no apparent alteration in mdm2 protein expression (abstract, p.983, p.984, first column, first two lines of third paragraph, and table II on page 983).

Quesnel B et al teach that in myelodysplastic syndrome, there is no amplification, nor over-expression of mdm2 gene (p.415, first column, first three lines of second

paragraph). Quesnel B et al teach that in haematological malignancies, such as leukemia and lymphoma, there is no amplification of mdm2, and an over-expression of mdm2 is found only in a small proportion of the cases (Abstract, and pp.415, 417).

Lee JM et al teach that p53 could induce apoptosis and cell cycle arrest, and that loss of p53 function causes increased resistance to chemotherapeutic agents (abstract). Lee et al teach that p53 functions as a transcriptional factor, via binding to specific DNA (p. 150).

It would have been prima facia obvious to use the peptide taught by Bottger et al to disrupt the binding of p53 and mdm2 in tumor cells, to increase the activity of p53, as taught Bottger et al. It would have been obvious to target any cancer cells that express p53 and mdm2, including those populations of cancer cells that do not overexpress mdm2, such as in breast cancer cells, taught by McCann et al or haematogical malignancies, taught by Quesnel B et al, because loss of p53 function is correlated with increased resistance to chemotherapeutic agents, as taught by Lee et al.

One would have been expected that the peptide does not inhibit the DNA specific binding property of p53, and that p53 is activated for DNA specific binding and transcription, because the peptide taught by Bottger et al disrupts the binding of p53 to mdm2 only at the specific p53 binding site to mdm2, as taught by Bottger et al, which is expected to be different from the DNA binding site of p53, and because the activity of p53 is to function as a transcriptional factor, via binding to specific DNA , as taught by Lee et al and Bottger et al .

One of ordinary skill in the art would have been motivated to disrupt the binding of p53 and mdm2 in cancer cells that express p53 and mdm2, including those populations of cancer cells that do not overexpress mdm2, with a reasonable expectation of success.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

October 06, 2005